MICROALBUMINURIA IN NON-DIABETIC ACUTE ISCHAEMIC STROKE: PREVALENCE AND PROGNOSTIC SIGNIFICANCE

Dissertation submitted for

M.D. GENERAL MEDICINE

BRANCH 1-DEGREE EXAMINATION MARCH 2007

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI.

MADRAS MEDICAL COLLEGE & GOVERNMENT

GENERAL HOSPITAL

CHENNAI- 600 003.

CERTIFICATE

Certified that this dissertation entitled "**Microalbuminuria in Acute Ischemic Stroke"** is a bonafide work done by Dr. M. Mohammed Safeer, Post Graduate of Internal Medicine, Institute of Internal Medicine, Madras Medical College, Chennai 600 003 during the academic year 2004 – 2007.

Prof.Dr.P.Thirumalaikolundusubramanian,
Director and Professor,
Institute of Internal Medicine,
Madras Medical Medical College &
Government General Hospital,
Chennai 600003

Prof.Dr.KalavathyPonniraivan,
The Dean,
Madras Medical College,
Chennai 600 003.

DECLARATION

I solemnly declare that this dissertation entitled " Microalbuminuria in Acute Ischemic Stroke" was done by me at Madras Medical College, Government General Hospital during 2004 – 2007 under the guidance and supervision of Prof. L. Pari, the former Director (I/c) of Institute of Internal Medicine, Madras Medical College. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree Branch I in General Medicine.

Place: Dr. M. Mohammed Safeer.

Date:

ACKNOWLEDGMENT

At the outset, I thank Prof. Dr. Kalavathi Ponniraivan, The Dean, Madras Medical College, Government General Hospital for having permitted me to use the facilities of the hospital for this study.

I sincerely acknowledge the contributions of Prof. Dr. L. Pari, the former Director (I/c) of Institute of Internal Medicine, Madras Medical College, in guiding and advising me regarding this study.

I am extremely indebted to my chief Prof. Dr. P. Thirumalaikolundusubramanian, The Director and Professor, Institute of Internal Medicine, Madras Medical College for his constant inspiration and in revising and supervising this study.

I express my sincere thanks to Dr.K.V.S Latha, Dr.R. Penchalaiah and Dr.P.Vijayaraghavan, Asst. Professors of Internal Medicine, Madras Medical College, for helping and supporting me in this study.

Last but not the least , I am extremely grateful to my patients without whose cooperation and support, this study would not have been possible.

CONTENTS:

INTRODUCTION

MicroAlbuminuria (MA) is defined as urine albumin excretion rate of 30 to 300 mg/day or 20 – 200 µg/min in a randomly collected sample.

MicroAlbuminuria is thought to be a marker of widespread vascular damage and reflects the systemic transcapillary leakage of albumin.

The significance of MicroAlbuminuria in relation to Diabetes has been extensively studied and documented in literature. The structural, functional and biochemical aspects contributing to MicroAlbuminuria is the basis of numerous past and ongoing studies. The prevalence, progression and regression of MicroAlbuminuria in various disease processes like diabetes, hypertension and coronary artery disease was repeatedly investigated in several land mark trials and have confirmed its significance.

There are a few published studies from West on MicroAlbuminuria in Cerebrovascular diseases. Observations made out of these studies confirm the association of MicroAlbuminuria in cerebrovascular disease similar to those in vascular disorders of Heart and Kidney. Unfortunately such reports are lacking from our country.

Hence an attempt has been made to study MicroAlbuminuria among Non–diabetic cerebrovascular accident patients from this part of the country.

ABBREVIATIONS

MA –MicroAlbuminuria

MI –Myocardial Infarction

DM –Diabetes Mellitus

HTN–Hypertension

TIA –Transient Ischemic Attack

AVM–ArterioVenous Malformation

ESR –Erythrocytic Sedimentation Rate

CT –Computed Tomogram

MR –Magnetic Resonance

GCS –Glasgow Coma Scale

LVH –Left Ventricular Hypertrophy

UAE–Urine Albumin Excretion

PCR–Protein Creatinine Ratio

ACR–Albumin Creatinine Ratio

CBF–Cerebral Blood Flow

CBV–Cerebral Blood Volume

DWI–Diffussion Weighted Imaging

PWI–Perfusion Weighted Imaging

NAA–N Acetyl Aspartate

AIM OF THE STUDY

1. To estimate the prevalence of Microalbuminuria in Non–Diabetic Acute Ischemic Stroke.

2. To assess the prognostic significance of Microalbuminuria in these cases with reference to Glasgow coma scale of the patient.

REVIEW OF LITERATURE

MICROALBUMINURIA

Historical Aspects

In 1963 Harry Keen was looking to document the earliest sign of renal disease in the Bedford survey. Clinical proteinuria was the hallmark of nephropathy but he wanted to measure the smallest amount. At a British Diabetic Association meeting Harry and his colleague Costis Chlouverakis heard the description of the method of measuring the amount of insulin by precipitating the amount of insulin – insulin – Antibody complex with the second, antiglobulin antibody. Soon they immunized a few guinea pigs with human albumin and with in a few months had discovered microalbuminuria (29).

Surprisingly the Ames company in 1950s, introduced the 'Albutest' for urine protein but it was immediately withdrawn since clinicians complained that it came out with false positive results in whom the standard sulphosalicylic test was negative. In fact the Albutest was so sensitive that it was detecting Microalbuminuria .

By 1982 MicroAlbuminuria was shown to a marker of early nephoropathy(30) and later a more general indicator of a bad blood vessels.

Since then the methodologies for detecting MicroAlbuminuria has grown by leaps and bounds with increasing sensitivity and specificity. The role of MicroAlbuminuria from a simple marker of early nephoropathy, has now changed to a harbinger for predicting the development and prognosis of vascular diseases of Heart, Brain, Kidney as well and as a marker of severity of inflammatory process in various settings.

EPIDEMIOLOGY

Urinary albumin excretion measurement was undertaken in multitude of varying studies in all continents and was found to be equally varying across different classes, age group, diseased and normal individuals.

AGE, GENDER AND ETHNIC VARIATIONS

Advanced age and male sex were more frequently seen in patients with increased levels of albuminuria (31). MicroAlbuminuria in general population studied in Britain was found to vary widely between Ethnic groups and ranged between 2.2–10.2%(1,2). Prevalence as high as 39 and 42% was found in Aborigine men and women respectively(3).

MICROALBUMINURIA IN DIABETES

MicroAlbuminuria in Type I Diabetes was found to be prevalent in 3.7 – 40% and in Type II Diabetes between 30 – 40% (4,5,6). The duration of diabetes was significantly longer in microalbuminurics than normoalbuminurics.

In the micro – HOPE study, MicroAlbuminuria was detected in

32.2% in diabetic participants and 14.7% in non – diabetic participants. Age, waist to hip ratio, diabetes, hypertension, smoking, vascular disease and LVH were independent determinants of MicroAlbuminuria in all participants (5). Mykkanen et al (7) in a study of 1449 patients showed a higher prevalence of MicroAlbuminuria in diabetes (27.6%) than in non–diabetes (13.9%).

MICROALBUMINURIA IN HYPERTENSION

MicroAlbuminuria in hypertensives was found to be prevalent in 3–37.5% patients in various studies(8,41).

MICROALBUMINURIA IN STROKE

Prevalence of MicroAlbuminuria in acute stroke was found to be between 30–46%. MicroAlbuminuria in non–diabetic stroke was found to be about 46% compared to 13.5% in controls studied several months after stroke.The prevalence of MicroAlbuminuria was 3 fold greater in patients with recent stroke when compared to controls with the same profile of cardiovascular risk factors (9,10).

The PREVEND (Prevention of REnal and Vascular ENd Stage Disease) study (31) prospectively studied the natural course of MicroAlbuminuria in inhabitants of The city of Groningen (The Netherlands) between the age group of 28 to 75 years and came up with the following findings:-

Table No – 1:PREVEND STUDY

Urinary Albumin Excretion	0-10 mg/L (n=30,670)	10-20 mg/L (n=6,749)	20-200 mg/L (n=2,918)	>200 mg/L (n=282)	Total (n=40,619)
Age, Year, Mean (S.D)	49.4 (12.7)	47.9(12.9)	53.1 (13.2)	57.2(12.7)	49.5(12.9)
Male, %	43.4	51.5	53.8	59.2	45.6
Morning Urine Albumin,Median	4.9	12.7	32.7	351.0	6.1
(25^{th}-75^{th} percentile)	(3.2-6.9)	(11.1-14.9)	(24.6-54.0)	(254.0-654.0)	(3.8-9.9)
Diabetes, %	2.1	2.9	6.2	17.6	2.6
Hypertension, %	10.3	10.9	18.9	38.1	11.2
Hyperlipidaemia, %	4.5	4.4	6.7	17.2	4.7
Positive family history of Cardiovascular Disease, %	32.0	31.7	33.2	40.9	32.1
Smoking, %	40.0	48.8	49.4	48.2	42.2
Myocardial infraction, %	2.7	2.8	6.0	11.0	3.0
Stroke, %	0.7	0.8	1.6	4.7	0.8

In this study, the age and sex adjusted prevalence of MicroAlbuminuria in Diabetic, hypertensive and in non–diabetic non–hypertensive subjects was 16.4, 11.5 and 6.6 % respectively. Advanced age, male sex, hyperlipidaemia, smoking, myocardial infarction and stroke were more frequently seen in subjects with

increased levels of albuminuria.

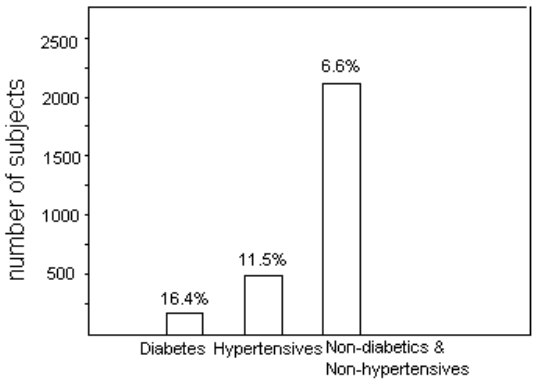


Figure 1. Age and Sex adjusted Prevalences of Microalbuminuria in diabetic, in Hypertensive, And in Non-Diabetics& Non-Hypertensive subjects.

MICROALBUMINURIA AS PREDICTOR OF OUTCOME

MICROALBUMINURIA IN VASCULAR DISORDERSS

The association of MicroAlbuminuria with other atherosclerotic risk factors such as diabetes, hypertension, dyslipdaemia and smoking is well known. MicroAlbuminuria doubles the risk of cardiovascular morbidity and mortality and doubles the risk of total mortality in diabetes (8,11,12).

Persistent MicroAlbuminuria in diabetic patients correlates with the presence of HTN, obesity and dyslipidaemia. Hypertensive patients with MicroAlbuminuria more frequently develop LVH and renal insufficiency. Several studies have revealed the significance of MicroAlbuminuria as a predictor of increased mortality in hypertensive patients and in elderly persons (1,13,14).

MicroAlbuminuria is detected early in the course of acute MI and is considered an independent predictor of early mortality in the condition.

It is of interest to note that MicroAlbuminuria may even precede manifest DM, HTN, Coronary Artery Disease(CAD) and stroke. MicroAlbuminuria may be considered as one of the earliest manifestation of insulin resistance syndrome(15).

Epidemiological studies suggest that MicroAlbuminuria can be regarded as a predictor of ischemic stroke in diabetic and non – diabetic subjects. The thickness of intima – media complex in the carotid arteries, which reflect the progression of ahterosclerosis in these vessels correlate well with the presence of MicroAlbuminuria (7,9).

PROGMOSTIC SIGNIFICANCE OF MICROALBUMINURIA IN STROKE

MicroAlbuminuria was found to be reliable predictor of higher mortality 3 months after stroke in studies on its prognostic significance in acute ischemic stroke (10).

MICROALBUMINURIA IN INFECTION, INFLAMMATION AND TRAUMA

In a study of acute Pancreatitis MicroAlbuminuria peaked at 36 hrs. after admission and serious complication developed later only in those patients with highest level of MicroAlbuminuria, regardless of serum amylase concentration (37).

MicroAlbuminuria helped to distinguish bacterial from aseptic meningitis with a specificity of 94% (39).

In elective surgery, MicroAlbuminuria measurement displayed large and more persistent rise in patients who later developed serious complications(38).

Measurement of MicroAlbuminuria in trauma victims 8 hrs after admission predicted the development of ARDS with positive predictive value of 85% and negative predictive value of 95%(36).

MICROALBUMINURIA IN CRITICALLY ILL

Measurement of MicroAlbuminuria may have role in early identification of patients at increased risk of developing Multiple System Organ Failure (MSOF) possibly leading to death i.e. within 6 hrs after admission to I.C.U. This is much earlier than current clinical scoring system can be used(33).

PATHOPHYSIOLOGY OF MICROALBUMINURIA

The pathogenetic mechanism implicated in MicroAlbuminuria includes intraglomerular hypertension, increased filtration fraction of albumin, decreased tubular reabsorption of albumin and increased glomerular hydrostatic pressure.

ELECTRON MICROSCOPIC STUDIES

Electron microscopic structural studies in non–albuminuric, micro–albuminuric and proteinuric patients reveal that glomerular basement membrane width and mesangial fractional volume increase and surface density of peripheral glomerular basement membrane decrease with increasing severity in the albumin excretion rate but with considerable overlap among groups. The strongest structural correlation with increased urine albumin excretion was attributed to mesangial fractional volume (16).

MICROALBUMINURIA AND ATHEROSCLEROSIS

Accumulating evidence suggests a common pathogenetic mechanism for MicroAlbuminuria and premature atherosclerosis, i.e. qualitative alterations of the extracellular matrix including decreased density and sulfation of Heparan Sulfate – ProteoGlycan (HS–PG) complex. Decreased density of HS in the glomeruli may lead to loss of charge selectivity, albuminuria and mesangial proliferation. In the intima of large vessels, decreased density and/or sulfation of HS may enhance several of the processes involved in premature ahterosclerosis. Diabetes affects the composition and structure of extracellular matrix in many ways and lead to decreased density and sulfation of HS – PG by several mechanisms. Genetic differences in the sulfation of HS and/or genetic differences in the coordinated biosynthesis of HS – PG might contribute to decreased concentration and sulfation HS – PG in susceptible individuals(17).

Endothelium dependent as well as endothelium independent vasodilatation was found to be significantly impaired in diabetes

especially in those with MicroAlbuminuria. The demonstration that MicroAlbuminuria diminishes promptly with short–term reduction in arterial BP argues that reversible haemodynamic factors play an important role in the pathogenesis of MA (18).

MECHANISM OF MICROALBUMINURIA IN ACUTE STROKE

The mechanisms determining the occurrence of MicroAlbuminuria in acute ischemic stroke have been studied in relation to biochemical markers of stress and inflammatory reactions as well as markers of endothelial damage including haematocrit, ESR, plasma glucose, fibrinogen, leukocytosis, thrombocytosis, vonwillebrand factor activity, IL – 6 and urinary epinephrine and nor epinephrine. Significant association has been found with vonwillebrand factor activity, urinary epinephrine on day 1 and serum IL – 6 in varying studies (19,20,21).

DETECTION OF MICROALBUMINURIA

The test include

A. Immunoturbidimetric method – Depends on the turbidity of solute when albumin in the sample of urine reacts with specific antibody. The turbidity is measured with a spectrophotometer and absorbance is proportional to the albumin concentration.

B. Immunonephelometric method – Albumin in the urine sample form light scattering antigen – antibody complex when it reacts with specific antibody which can be measured with laser nephelometer.

C. Radioimmunoassay – Albumin in the urine sample competes with a known amount of radiolabelled albumin for fixed binding sites of antibodies. Free albumin can be separated from bound albumin by immuno – adsorption of the albumin bound antibody. Albumin concentration in the sample is inversely proportional to radioactivity.

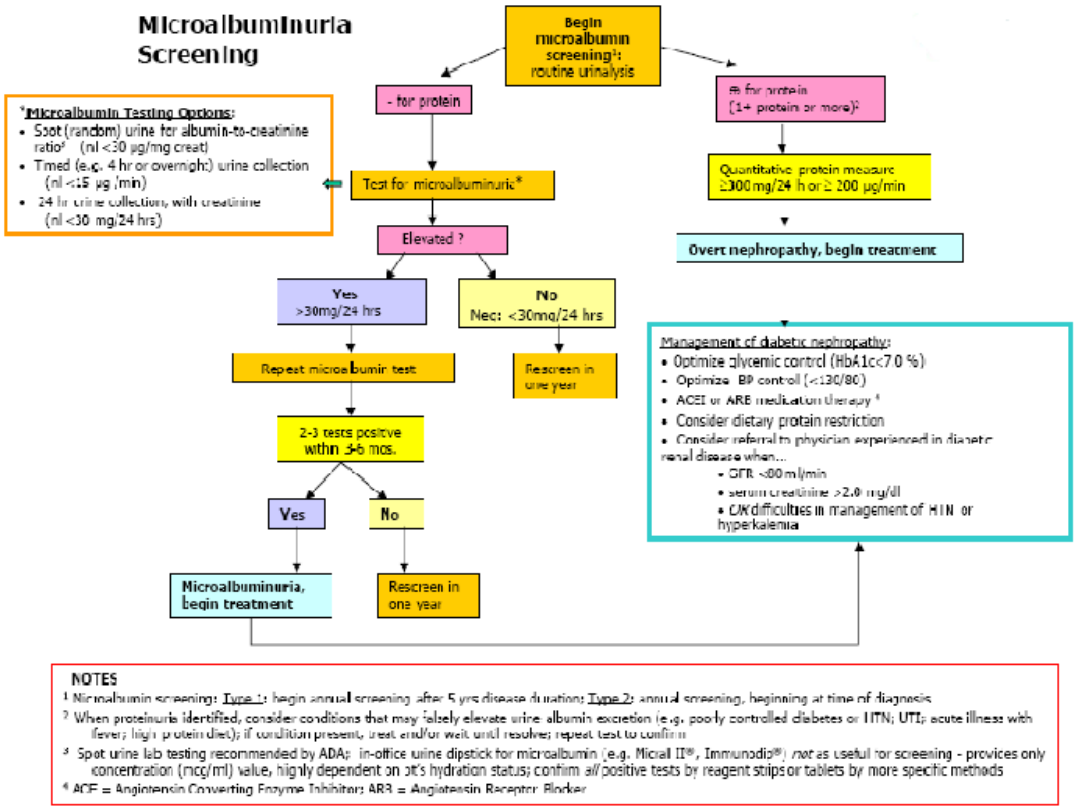
D. ELISA – Competitive ELISA can also be used for testing MicroAlbuminuria.

The tests mentioned so far measure the total protein or albumin concentration. In an effort to correct for problems relating to variability in urine volume and concentration, many investigators use the Protein Creatinine Ratio(PCR) or Albumin Creatinine Ratio(ACR) in Random or Timed volume collection. There is high degree of correlation between 24 hrs urine protein concentration and PCR.

SCREEING FOR MICROALBUMINURIA

Considering the importance of MicroAlbuminuria in various disease processes, screening for MicroAlbuminuria is acceptable in clinical practice. In fact, annual screening for albuminuria in patients with diabetes is recommended in the guidelines of American Diabetes Association (ADA). Screening may also be contemplated in patients with Hypertension, Hyperlipidaemia and those who smoke. The report that MicroAlbuminuria may precede manifest Diabetes, Hypertension, Coronary artery disease and Stroke raise serious doubt whether we should limit our screening strategies to those with known risk factors or preferably should screen general population(5).

SCREENING STRATEGY



NEWER SCREEING METHODS

In addition to the measurement of Albumin to Creatinine ratio or Albumin concentration in a Random or Timed Urine Samples, an array of newer screening tests are being developed to test MicroAlbuminuria. These include the MICRAL – II test and Immunodip test.

Multicentre trials show that MICRAL – test II immunologic test strips permits an immediate and reliable semiquantitative determination of low albumin concentration with an almost user

independent colour interpretation (22). But considering the higher cost of MICRAL strips and the better sensitivity and specificity of the measurement of Urine Albumin Concentration or Urine Albumin to Creatinine ratio, the latter may still be the test of choice for screening for MA (23).

THERAPEUTIC IMPLICATIONS OF MICROALBUMINURIA

Angiotensin Converting Enzyme Inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARB), are the most effective in lowering urine albumin excretion. It has been shown in many patients with manifest renal disease that in those with overt proteinuria of more than 300 mg/day, the extent to which proteinuria is lowered during treatment predicts the prevention of both chronic kidney disease and cardiovascular disease. It is likely that the same holds true for microalbuminurics also (24,25).

RELEVANCE OF THE STUDY

The measurement of MicroAlbuminuria is a simple quick and non invasive technique that is showing promise as an early and sensitive indicator of disease severity in a range of clinical conditions. If so, MicroAlbuminuria shall prove to be useful for targeting early and aggressive treatment in those prone for severe complication and outcome.

CEREBROVASCULAR DISEASE

Cerebrovascular diseases include some of the most common and devastating disorders – ischemic stroke, hemorrhagic stroke and cerebrovascular anomalies such as intracranial aneurysm and Arterio Venous Malformations (AVM). The incidence of cerebrovascular disease increase with age.

ISCHEMIC STROKE

Cerebral ischemia is caused by a reduction in blood flow that lasts more than several seconds since neurons lack glycogen. When blood flow is quickly restored, brain tissue can recover fully and the symptoms are only transient; this is called Transient Ischemic Attack(TIA). Typically the neurological signs and symptoms of TIA last for 5 – 15 minutes but by definition must last less than 24 hrs.

If the cessation of blood flow lasts for more than a few minutes, infarction of brain tissue results. Stroke has occurred if the neurologic signs and symptom last for more than 24 hrs.

CAUSES OF ISCHEMIC STROKE

Focal ischemia or infarction is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal source either an artery or heart.

Cardioembolism is responsible for 20% of all ischemic stroke. Emboli from heart most frequently lodge in the Middle Cerebral Artery (MCA), the Posterior Cerebral Artey (PCA) or one or its branches and infrequently the Anterior Cerebral Artery (ACA). The significant cause of cardioembolism include Rheumatic Heart

Disease (RHD),Non–rheumatic Atrial Fibrillation, Myocardial Infarction, prosthetic valves and cardromyopathies.

Thrombus formation in atherosclerotic plaques in extracranial arteries can embolise to intracranial arteries produce an **Artery to Artery** Emboli stroke. The most common source of embolism is the carotid bifurcation.

Intracranial atheroselerosis produce stroke either by an embolic mechanism or **in situ** thrombosis of diseased vessels.

Other less common cause of stroke include Dissection of internal carotid arteries, vertebral vessels beyond the arch of Willis as may occur in Ehler–Danlos type IV, Marfan's syndrome, cystic medial necrosis and fibromucular dysplasia; Hypercoagulable states like protein C and S deficiency; factor V Leiden mutation, polycythaemia and sickle cell anemia; Fibromuscular dysplasia; giant cell arteritis; Wegener's granulomatosis; Moyamoya disease; Reversible posterior leukencephalopathy; Binswanger disease (Chronic progressive subcortical encephalopathy); CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarct and Leukencephalopathy)(40).

IMAGING STUDIES IN ACUTE ISCHEMIC STROKE

CONVENTIONAL COMPUTED TOMOGRAM(CT)

The major role of the unenhanced CT is to exclude the haemorrhagic lesion. Conventional CT may be normal within 6 hrs. of symptom onset and early CT hypodensity represents tissue that is doomed for irreversible infarction.

MULTIDETECTOR CTs

Include CT Angiogram(CTA) and CT Perfusion studies (CTP). CTA is a very good tool to evaluate the vascular status of the neck and intracranial vessels.

CTP studies use several parameter maps like the Time to Peak Map (TTP), the Mean Transit Time (MTT) Map, the Cerebral Blood Flow(CBF) Map and the Cerebral Blood Volume(CBV) Map. The Timed Maps are very sensitive to haemodynamic abnormality while the CBF and CBV maps predict the outcome of ischemic lesion.

CONVENTIONAL MAGNETIC RESONANCE (MR) IMAGING

Conventional MRI though reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and the cortical surface; it is less sensitive to detect acute blood. Besides, it is quite insensitive to acute ischemic change. Magnetic Resonance Angiogram(MRA) visualizes the cerebrovascular anatomy non–invasively without any radiation hazard.

DIFFUSION WEIGHTED IMAGING (DWI)

Areas of Diffusion Weighted Imaging (DWI) changes or significant reduction in the Apparent Diffusion Coefficient (ADC) were thought to represent irretrievable tissue i.e. they generally represent areas of limited reversibility. DWI studies

are more sensitive to acute ischemic change.

PERFUSION WEIGHTED IMAGING (PWI)

MR Perfusion Weighted Imaging (PWI) studies using gadolinium contrast are interpreted by various parameters. Most centers generally use a qualitative analysis of the most sensitive time map to evaluate the extent of perfusion abnormality.

DIFFUSION – PERFUSION MISMATCH

Ischemic Penumbra has been defined as the mismatch between the diffusion – perfusion abnormalities. A significant mismatch has been operationally defined as "at least 20% discrepancy between the smaller DWI lesion and the larger PWI lesion in their volume".

MAGNETIC RESONANCE (MR) SPECTROSCOPY

Proton MR Spectroscopy measure several brain metabolites including N Acetyl Aspartate (NAA) and lactate. NAA decreases steadily to 50% of the base line value six hours after symptom onset. Lactate is a product of anaerobic glycolysis that rises once the Cerebral Blood Flow (CBF) decreases below 20ml/100gm/min. Ischemic penumbra is defined as an area with an elevation of lactate without any significant decrease of NAA.

POSITRON EMISSION TOMOGRAM (PET)

PET uses Radiotracers like Oxygen15, Carbon11– Flumazenil or Fluoro Misonidazole (F18-MISO) and it assess the ischemic penumbra by mapping out areas of increased Oxygen Extraction Fraction (OEF) ranging from the normal value (0.3–0.4) with a preserved Cerebral Metabolic Rate of Oxygen (CMRO2).

SINGLE PHOTON EMISSION COMPUTED TOMOGRAM (SPECT)

SPECT uses tracers like Technetium Hexa Methyl Propylene Amino Oxime (HMPAO) and Technetium Ethyl Cysteinate Dimer (ECD) to demonstrate the location, size and extent of the Cerebral Blood Flow (CBF) abnormality after the onset of ischemia.

TRANS CRANIAL DOPPLER (27)

Trans Cranial Doppler (TCD) is a technique to define Cerebral Blood Flow Velocity (CBFV) within vessels at the skull base non–invasively. TCD has almost 100% sensitivity in acute phase of stroke. The specificity of TCD is very high with proximal occlusion as in carotid or Vertebral arteries as well as in Middle Cerebral Artery occlusion. TCD specificity in Anterior Cerebral or Posterior Cerebral Artery territory stroke is relatively low. TCD has a high negative predictive value and it may prevent cerebral angiography.

TREATMENT OF ACUTE ISCHEMIC STROKE:

ANTIPLATELET AGENTS –

Aspirin as a non–specific cox inhibitor has been widely used in low doses. It blocks TXA2 formation.

Ticlopidine and clopidogrel block the Adenosine Di Phosphate(ADP) receptor on platelets preventing the cascade of activation of GP II b/III a receptor that leads to fibrinogen binding to platelets.

Dipyramidole inhibits the uptake of adenosine by platelets and vascular endothelial cells, thereby causing accumulation of

adenosine, which is an inhibitor of platelet aggregation.

GP IIb/III a receptor antagonist may have potential application for the treatment of acute ischemic stroke and as adjunctive therapy to carotid angioplasty.(28)

RECANALISATION THERAPIES

Thrombolysis

Intravenous Thrombolysis

The National Institute of Neurological Disorders and Stroke (NINDs) study showed that administration of rtPA within 3 hours of onset of symptom of acute ischemic stroke caused 30% reduction of mortality in 3 months (34).

Intra arterial thrombolysis trials

The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial on the clinical efficacy of direct intrarterial infusion rPro UroKinase found a 10–12% absolute increase in positive neurological outcome compared with placebo group at 90 days.

ASSESSMENT OF NEUROLOGIC DEFICIT IN STROKE

Various methods exist for assessing level of consciousness in acute stroke clinical trials including the National Institute of Health (NIH), Scandinavian Stroke Scale (SSS) and European stroke scale. The relationship between Glasgow Coma Scale (GCS) and stroke outcome has been studied by a Weir et al (32) and was found that each of the component was strongly related to outcome. Multivariate analysis of individual GCS component identified the verbal and eye component as the best predictors of clinical relevant

outcomes. Addition of the eye to the verbal component improved sensitivity although specificity was decreased.

The verbal score in GCS contain valuable prognostic information and should be recorded even in dysphasic patients. The maximum verbal score of 5, corresponding to a mentated verbal response accurately predicted 2 weeks survival and good 3 months outcome.

MATERIALS AND METHODS

Setting

This study was done in the inpatient setting of Department of Internal Medicine, Government General Hospital, Chennai.

Study Design

Single center Cross sectional study

Period of study

March-December 2005

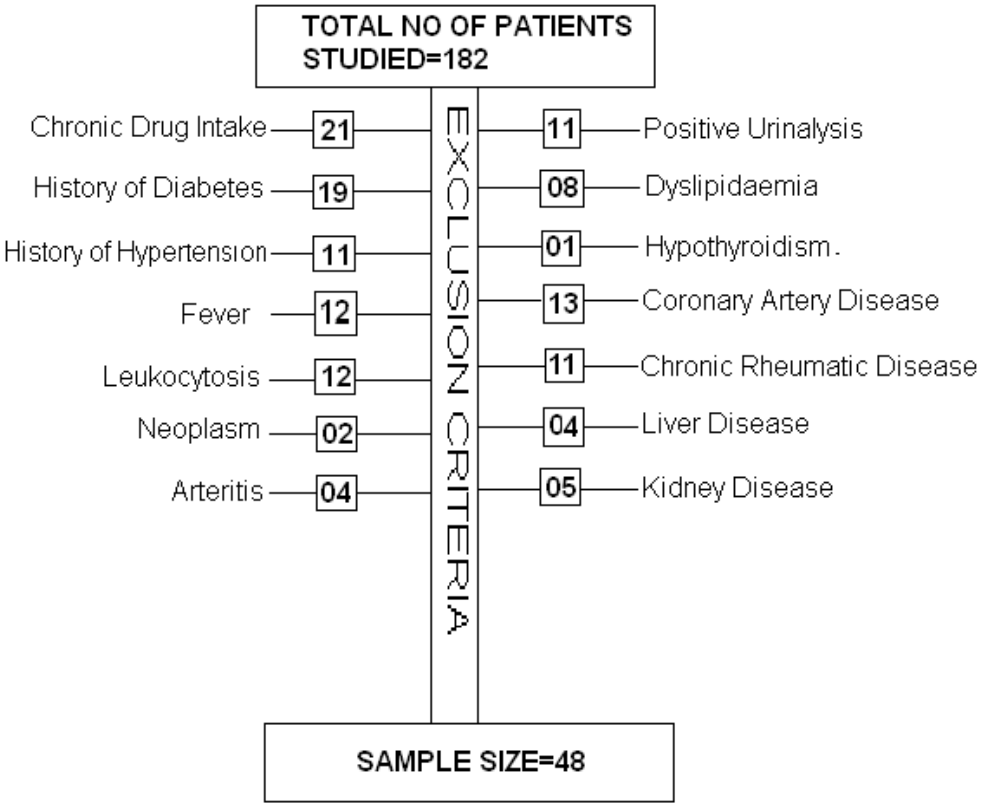
Collaborating Departments

The study was done with the help of Department of Biochemistry for various biochemical parameters and Department of Radiology for computed Tomography of the brain to confirm the presence of acute ischemic stroke.

Selection of study subjects

The study subjects were selected from a total sample of 182 patients admitted with acute ischemic stroke presenting within 24 hours of stroke onset. They were carefully analysed for the exclusion criteria after which the sample size shrunk to 48.

PATIENT'S FLOW CHART



Inclusion Criteria

The patient profile studied included both males and females aged from 25-83 years admitted within 24 hours of onset of acute ischemic stroke as confirmed by computed Tomography.

Exclusion Criteria

The Exclusion Criteria was fairly rigid, it was:

1. positive urine analysis including Haematuria, Pyuria, Proteinuria, Glycosuria
2. Kidney diseases both congenital and acquired
3. Diabetes Mellitus
4. Liver disease
5. Chronic Inflammatory Gastrointestinal disorder
6. Neoplasm
7. Any sign of infection
8. Coronary Artery Disease or Acute Coronary event
9. Other congenital or endocrine disorder
10. Inflammatory Rheumatic disease
11. Dyslipidemia
12. Those on Non-steroidal Anti-inflammatory drugs or Immunosuppresants
13. Fever
14. Other chronic infective or inflammatory disorders
15. History of Hypertension

Details of study subjects

Demographic data

The study group included patients from all over Tamil Nadu and adjacent states in keeping the status of the institution as a tertiary care referral centre

Clinical and Laboratory Details

All patients on admission had their history taken and underwent a thorough clinical check up. The severity of the neurological deficit was assessed according to the Glasgow Coma Scale.

The patient or the caregiver was interviewed to establish the past medical and personal history.

All patients had their Blood Pressure and Electrocardiogram taken.

Acute ischemic stroke was documented by computed tomogram

Blood Glucose levels were measured on day 1 and serially on days 3,5 and 7. Haematocrit, WBC count, Blood Urea, Serum Creatinine and Electrolytes and Lipid profile of the patients were also noted.

The Alubmin Excretion Rate was assessed in a 24 hours Urine collection performed on day 2. Urine Albumin Excretion was done by the IMMUNOTURBIDIMETRIC METHOD. It was expressed as mg/day.

Definitions

A daily Urinary Albumin Excretion below 30 mg was considered to be within the normal range.

Microalbuminuria was defined as urine albumin excretion rate between 30 and 300 mg/day.

Proteinuria was defined as Urine albumin excretion rate of more than 300 mg/24 hours.

ECG evidence of Left Ventricular Hypertrophy(LVH) was assessed by the **Sokolow–Lyon** criteria taken as a deep S wave in V1 or V2 and a tall R wave in V5 or V6 with the sum of the two deflexions exceeding 35 mm.

Glasgow Coma Scale was assessed as follows:-

Eye opening	4-Spontaneously
	3-To verbal stimuli
	2-To pain
	1-Never
Best Verbal response	
	5-Oriented and converses
	4-Disoriented and converses
	3-Inappropriate words
	2-Incomprehensible sounds
	1-No response

Best motor response

6-Obeys

5-Localises pain

4-Flexion withdrawal

3-Abnormal flexion (decorticate rigidity)

2-Extension (decerebrate rigidity)

1-No response

Study Details

In the study, we primarily grouped the patient into **Group A** i.e. Patients with Microalbuminuria and **Group B** i.e. Patients without Microalbuminuria i.e. Normalbuminuric patients. This was to assess the prevalence of Microalbuminuria in Acute Ischemic Stroke.

These two study groups were then compared with reference to their Age, Gender, GCS, ECG evidence of LVH, Systolic and Diastolic Blood Pressure.

Significant correlation was sought between:

Urine Albumin Excretion and Age

Urine Albumin Excretion and Gender

Urine Albumin Excretion and Glasgow Coma Scale

Age and Glasgow Coma Scale.

Urine Albumin Excretion and Left Ventricular Hypertrophy.

Limitation of Study

The prognostic parameter studied was confined to Urine Albumin Excretion and GCS. Death or Functional outcome of the patient after treatment could not be followed up

As the study was conducted in a referral tertiary institute, there might be an inadvertent selection bias towards the seriously ill. The reproducibility of the same in wider settings needs to be investigated further.

Statiscal Analysis

The Statistical Analysis was done using a SPSS Statistical Software Package.

RESULTS

The study group included 48 patients.

Microalbuminuria was present in 23 of the 48 patients.

The study group was again divided into two basic groups that is

Group A – Patients with Microalbuminuria and

Group B – Patients without Microalbuminuria

of Left Ventricular Hypertrophy in ECG.

Intra–group comparisons and correlation studies were done

The baseline characteristics of the patients with Microalbuminuria and patients without Microalbuminuria are

given below in tables 2 and 3. These two groups were mainly compared in terms of their Age, Gender, GCS, Blood Pressure and presence/absence of Left Ventricular Hypertrophy.

Table No.2 - Baseline Characteristics in Patients with Microalbuminuria (Group A)

Sl.No.	NAME	AGE	SEX	SBP*	DBP#	LVH♣	GCS♦	UAE♠
3	S	62	M	160	100	+	5	118
5	S	54	M	156	90	-	10	86
7	S	58	M	180	110	-	9	48
9	R	54	M	140	80	+	3	144
10	S	60	M	170	114	+	5	124
12	S	56	M	200	100	+	4	92
13	A	70	M	146	92	-	9	88
14	M	50	M	140	80	-	14	76
16	C	43	M	170	124	+	6	
17	E	70	M	150	90	-	9	45
18	P	75	M	164	86	-	9	38
20	R	57	M	156	94	-	9	44
21	K	65	M	150	90	-	11	71
23	P	65	M	144	88	-	8	45
25	G	75	M	160	80	-	12	40
27	M	52	M	176	94	+	8	93
31	B	65	F	130	80	-	11	51
33	K	85	F	144	70	-	8	86
35	B	75	F	160	108	+	9	79
40	G	50	F	154	92	-	10	58
43	R	65	F	170	100	-	9	48
44	P	80	F	140	90	-	7	117
45	C	85	F	170	116	-	6	92

∗ Systolic Blood Pressure # Diastolic Blood Pressure ♦ Glasgow Coma Scale

♣ Left Ventricular Hypertrophy ♠ Urine Albumin Excretion

Table No.3 - Baseline Characteristics in Patients without Microalbuminuria(Group B)

Sl.No.	NAME	AGE	SEX	SBP*	DBP#	LVH♣	GCS♦	UAE♣
1	A	45	M	150	96	-	11	18
2	C	46	M	164	106	+	11	10
4	M	45	M	140	86	-	12	19
6	K	72	M	138	92	-	11	26
8	K	55	M	154	100	-	10	28
11	M	63	M	146	92	-	10	15
15	E	45	M	156	80	-	12	13
19	R	58	M	170	96	+	13	14
22	C	55	M	160	90	-	8	13
24	D	58	M	148	82	-	10	17
26	A	50	M	136	70	-	8	14
28	C	50	M	140	90	-	11	10
29	S	47	M	150	80	-	12	28
30	V	45	M	148	96	-	13	23
32	S	67	M	150	100	-	10	16
34	V	40	F	130	84	-	13	7
36	C	65	F	154	90	-	14	18
37	V	61	F	160	80	-	14	19
38	R	50	F	164	104	+	13	26
39	V	60	F	170	80	-	13	20
41	V	25	F	150	90	-	11	18
42	R	65	F	166	110	+	14	11
46	A	55	F	150	94	-	13	15
47	M	65	F	140	80	-	14	12
48	K	70	F	130	100	-	13	17

* Systolic Blood Pressure # Diastolic Blood Pressure

♣ Left Ventricular Hypertrophy ♦ Glasgow Coma Scale ♠ Urine Albumin Excretion

Table No.4 - Baseline Characteristics and outcome in Patients with and without MicroAlbuminuria (MA)

Category		Patient with MA	Patient without MA
No. of Cases		23	25
Age (Mean)		63.96 ± 11.93	54.28 ± 10.86
Gender in percentage	M	17(73.91%)	15(60%)
	F	6(26.08%)	10(40%)
Systolic BP (Mean)		157.83 ± 16.01	150.56 ± 11.50
Diastolic BP (Mean)		94.26 ± 13.27	90.72 ± 9.76
ECG with LVH		(30%)	(16%)
Urine Albumin Excretion		78.17 ± 31.02	17.01 ± 5.69
Glasgow Coma Scale		8.30±2.62	11.76±1.76

Patients with Microalbuminuria (Group A) & Patients without Microalbuminuria (Group B) were compared with reference to sample sizes, Age, Gender, Systolic BP, Diastolic BP, ECG evidence of left ventricular hypertrophy & Glasgow Coma Scale as given in Table 4.

Table No.5 – UAE♣ in Patients Studied

Category of Cases	Number of Cases	UAE in mg / day			
		Mean ± SD	Median	25th Percentile	75th Percentile
Patient with MA #	23	78.17 ± 31.02	79	48	93
Patient without MA #	25	17.01 ± 5.69	17	13	19
Whole Study group	48	46.35 ± 36.77	28	17	78

♣ Urine albumin Excretion

Micro albuminuria

P<0.001 (significant at 1 % level)

The Mean, Median, 25th & 75th percentile of the Urine Albumin Excretion of the patients in Group A & B was as given in Table 5

The mean Urine Albumin Excretion in patients with Microalbuminuria was found to be 78.17 ± 37.02.

The mean Urine Albumin Excretion in patients without Microalbuminuria was found to be 17.01 ± 5.69.

The mean Urine Albumin Excretion in the whole study group was found to be 46.35 ± 36.77.

Table No.6 – Glasgow Coma Scale (GCS) in Patients with MicroAlbuminuria (MA) and without MicroAlbuminuria (MA)

	GROUP A	GROUP B
	WITH MA	WITHOUT MA
	GCS#	GCS
Mean	8.30 ± 2.62	11.76 ± 1.76
Median	9	12
25th Percentile	6	11
75th Percentile	10	13

P < 0.001 -Significant at 1% level

#Glasgow Coma Scale

Glasgow Coma Scale of patients with and without MicroAlbuminuria was compared as given in table 6.

The mean GCS in patients in Group A was 8.30 ± 2.62.

The mean GCS in patients in Group B was 11.76 ± 1.76.

The mean GCS of patients in Group A was significantly lower than that of patients in Group B.

Table No.7 - Age in Patients with MicroAlbuminuria (MA) and without MicroAlbuminuria (MA)

	GROUP A	GROUP B
	WITH MA	WITHOUT MA
	AGE	AGE
Mean	63.96 ± 11.53	54.28 ± 10.86
Median	65	55
25th Percentile	54	46
75th Percentile	75	63

P < 0.001 –significant at 1%level

The age of patients in Group A & B were compared as given in Table 7

The mean age of patients in Group A was 63.96 ± 11.53

The mean age of patients in Group B was 54.28 ± 10.86

The mean age of patients in Group A was significantly higher in Group A than in Group B.

Table No.8 - Age in relation to Gender

		AGE in years			
		MEAN	MEDIAN	25TH PERCENTILE	75TH PERCENTILE
WITH MA (Group A)	MALE	60.65 ± 8.93	60	54	65
	FEMALE	73.33 ± 13.66	77.50	65	85
	COMBINED	63.96 ± 11.53	65	54	75
WITHOUT MA (Group B)	MALE	53.40 ± 8.75	50	45	58
	FEMALE	55.60 ± 13.87	60.50	50	65
	COMBINED	54.2 ± 10.86	55	46	63

The age of the patients in Group A & Group B were compared in relation to gender as given in Table 8

In Group A, the Mean Age of Male & Female patients were 60.65 ± 8.93 and 73.33 ± 13.66 respectively.

In Group B, the Mean Age of Male & Female patients were 53.40 ± 8.75 and 55.60 ± 13.87 respectively.

The Female in Group A were older than Males.

Table No.9 –Urine Albumin Excretion in Patients older than 60 years and younger than 60 years in Patients with and without MicroAlbuminuria

	GROUP A		GROUP B	
	WITH MA		WITHOUT MA	
	AGE Group		AGE Group	
	< 60	> 60	< 60	> 60
	UAE	UAE	UAE	UAE
MEAN	88 ± 32.97	70.62 ± 28.39	17.24 ± 6.25	16.75 ± 4.75
MEDIAN	89	71	17	16.50
25th Percentile	58	45	13	13.50
75th Percentile	115	80	20	18.50

P = .713 in PTS without MA < 60 yrs ; P = 0.696 in Patients with MA < 60

P = .202 in PTS without MA > 60 yrs ; P = .386 in Patients with MA > 60

An intra group comparison was made to find out any correlation of Urine Albumin Excretion with age as given in table 9.

Table No.10 – UAE in mg / day in relation to Gender

Category	Gender	Number of Cases	Mean ± SD	Median	25th Percentile	75th Percentile
Patients with MA	Male	17	77.53 ± 33.62	76	45	58
	Female	6	80.00 ± 24.73	82.50	93	92
Patients without MA	Male	15	17.60 ± 6.05	16	13	23
	Female	10	16.30 ± 5.33	17.50	12	19

P = 0.871 in Patient with MA

P = 0.087 in Patient without MA

The Urine Albumin Excretion (UAE) of Male & Female Patients was calculated separately as given in Table 10.

The Mean Urine Albumin Excretion of Male Patients in Group A was 77.53 ± 33.62.

The Mean Urine Albumin Excretion of Female Patients in Group A was 80.00 ± 24.73.

The Mean Urine Albumin Excretion of Male Patients in Group B was 17.60 ± 6.05.

The Mean Urine Albumin Excretion of Female Patients in Group B was 16.30 ± 5.33.

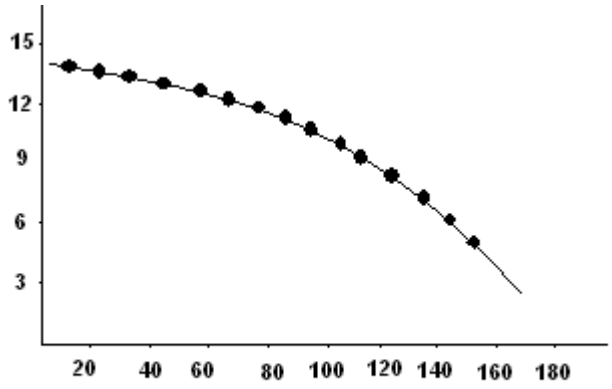
From this it can be deduced that Mean Urine Albumin Excretion of Females was slightly higher in Group A.

Table No.11 - Correlation coefficients of Age, UAE and GCS in Patients with MA

Category	UAE	GCS
AGE	Λ = - .1707 p = .436	Λ = .0366 p = .860
UAE	-- --	Λ = - .6895 p = .000*

*p < 0.01 – Significant at 1% level

Figure 2: Graph showing the relationship between GCS and UAE



The Correlation studies done with reference to Urine Albumin Excretion(UAE), Age and Glasgow Coma Scale(GCS) is given Table 11 and Figure 2

There is significant Correlation between Urine Albumin Excretion and GCS in Group A while no such correlation was found in Group B.

Table No.12 - Correlation Coefficients of Age, UAE & GCS in Patients Group B

Category	UAE	GCS
AGE	Λ = - .0636 p = .763	Λ = .1560 p = .457
UAE	- - - -	Λ = - .0103 p = 0.961

But there was no significant correlation between GCS and UAE in group B.

Table No.13 - Mean UAE in Relation to Presence / Absence of LVH

		CATEGORY			
		WITH MA		WITHOUT MA	
		No. of Cases	UAE mg/day	No. of Cases	UAE mg/day
LVH	Present	7	109.29 + 22.40	4	15.25 + 7.37
	Absent	17	64.56 ± 23.69	21	17.43 ± 5.47

P - 0.000* in Patients with MA * - Significant at 1% level

P - .495# in Patients without MA # - Not Significant

We also looked into correlation of Urine Albumin Excretion (UAE) with Left Ventricular Hypertrophy (LVH) as given in table 13

The patients with LVH in Group A had significantly higher Urine albumin excretion than patients without LVH.

DISCUSSION

The association of Microalbuminuria in cerebrovascular diseases has been confirmed in a few Western studies. This study was undertaken to analyze Microalbuminuria in acute cerebral ischemic events in our context. After analysis of 182 patients with reference to inclusion and exclusion criteria, 48 patients were selected for the study.

STRENGTH OF THE STUDY

My study was based on sample size of 48 subjects. Though the study size is relatively small, it may still be relevant since the exclusion criteria was fairly rigid including all patients with diabetes, history of hypertension, history of coronary artery disease or acute coronary event, any infective or inflammatory disorder, positive urine analysis, fever, history of chronic nonsteroidal anti inflammatory drug intake. The study was confined to patients with purely acute ischemic stroke. Therefore the crux of the study is the association of Microalbuminuria with acute cerebral infarction where other factors that may influence albumin excretion were excluded.

LIMITATION OF STUDY

Since the study was carried out in a tertiary care referral institute, the reproducibility of these findings in the same cohort of patients in a more general setting is to be investigated further.

Being a single centre cross sectional study, there might be an inadvertent selection bias towards the seriously ill and the lack of data regarding the final outcome of death

in this study may have its own pitfalls.

PREVALENCE OF MICROALBUMINURIA

In this study Microalbuminuria was present in 23 of 48 subjects, which amounted to prevalence of 47%. This was conforming to the past studies in acute cerebrovascular accidents. Previous studies are given in table 14.

Table 14- Prevalence studies of microalbuminuria in acute ischemic stroke

Study	Sample size	Prevalence in cases	Prevalence in controls	year	Journal
Turaj et al	52	46%	13%	2001	Med Sci Monit
Beamer et al	97	30%	10%	1999	Arch Neur

In both these studies, controls had similar risk factor profile to those with acute ischemic stroke studied including coronary artery disease and hypertension. These studies noted higher prevalence of microalbuminuria in acute stroke compared to risk factor adjusted controls.

Prevalence rate of Microalbuminuria in stroke is similar to that reported in other conditions. In diabetes the reported prevalence of Microalbuminuria was 3 to 40% (5,6,7). Hypertensives had a reported prevalence of 3 to 37%(8,31). This study had a relatively high prevalence of Microalbuminuria in acute phase of stroke.

PROGNOSTIC SIGNIFICANCE OF MICROALBUMINURIA

The prognostic significance of Microalbuminuria was studied in relation to Glasgow Coma Scale (GCS). Past studies (10) had shown significant correlation of Microalbuminuria with Scandinavian Stroke Scale (SSS) in acute Ischemic Stroke confirming its prognostic significance. We used a different scale that is the Glasgow Coma Scale to assess the severity of neurological deficit.

Glasgow Coma Scale and stroke outcome had significant correlation in past studies (32).

Mean Glasgow Coma Scale of patients with Microalbuminuria was significantly lower than that of patients without Microalbuminuria (8.30±2.62 vs 11.76±1.76). There was also a significant negative correlation of Glasgow Coma Scale with urine albumin excretion in our study (SeeTables 6 &11). The lower the Glasgow Coma Scale the more the urine albumin excretion and vice versa. Hence Microalbuminuria may be an important prognostic marker in stroke.

Therefore measurement of microalbuminuria may help to assess who is at increased risk and to triage those who may need a more aggressive management protocol.

AGE, GENDER AND URINARY ALBUMIN EXCRETION

The patients with Microalbuminuria were significantly older than the patients without Microalbuminuria in our study. This was also conforming to the past studies (10).

Past studies have shown significant association between albuminuria and advanced age (9,10,31).

But no significant graded correlation was found between age and urinary albumin excretion in both Microalbuminurics and normalbuminurics in our study. An intragroup analysis was also done i.e. by grouping the patients to less than 60 years and more than 60 years. Still urine albumin excretion and age defied a significant graded correlation.

We infer that urine albumin excretion might be much more dependent on the severity of the stroke process than age as evidenced by its significant correlation with Glasgow Coma Scale in acute stroke victims in microalbuminuria.

Female patients were older in our study. The mean age of female patient with microalbuminuria was 73.33 while that of male patients was 60.65.

The mean urine albumin excretion was slightly more in female subjects, which may be probably due to their advanced age.

The strong correlation of urine albumin excretion with Glasgow Coma Scale than with Age/Gender may be in part due to an acute phase inflammatory response (10).

Microalbuminuria as a marker of acute phase inflammatory response was documented earlier and it may also foretell the severity of acute phase response (33,35,36,37,39, 42).

AGE, GENDER AND GLASGOW COMA SCALE

There was no significant correlation of Glasgow Coma Scale in relation with the gender. Also there was no significant correlation between age and Glasgow Coma Scale in this study. Early studies

had mentioned a more severe correlation between the advancing age and a worse neurological deficit (10). This could not be identified in our study.

BLOOD PRESSURE AND MCIROALBIMINURIA IN STROKE

Blood Pressure is a confounding factor in stroke. In our study, patients with past history of hypertension came under exclusion criteria. But an elevated blood pressure is a frequent accompaniment in stroke. There was no significant difference in blood pressure in microalbuminirics and normalbuminurics in our study. There was also no correlation between blood pressure and urine albumin excretion in patient with or without microalbuminuria.

Studies have reported higher graded prevalence of microalbuminuria in hypertensives (24, 31). The plausible explanation is that there is a certain degree of acute dysautonomia in acute stroke events that may not reflect the actual blood pressure of the patient.

MICROALBUMINURIA WITH ELECTROCARDIOGRAPHIC EVIDENCE OF LEFT VERTRICULAR HYPERTROPHY

Microalbuminurics with ECG evidence of LVH had significantly higher rate of albuminuria in our study. No such correlation could be found in normalbuminurics.

7 out of 23 patients with Microalbuminuria had ECG evidence of LVH. These patients might have had systemic hypertension earlier which might have gone unrecognized and the higher albumin excretion in those with evidence of LVH may have occurred in the setting.

Hypertensives with Microalbuminuria were reported to have earlier onset of LVH and renal insufficiency (11,13,14).

Smoking and urine albumin excretion

No significant comparative studies could be made between smoking and albuminuria since the number of non–smokers among males studied was miniscule. Females who were all non–smokers had a higher mean albumin excretion, which might be due to a higher mean age of females in our study.

CONCLUSION

1. Microalbuminuria was present in 47% acute ischemic stroke patients studied.

2. Urine albumin excretion had the strongest correlation with the Glasgow Coma Scale of the patient in Acute Ischemic Stroke. Those with a lower Glasgow Coma Scale had a higher rate of urine albumin excretion and vice versa.

3. Acute ischemic stroke patient with Microalbuminuria were significantly older than Normalbuminurics but there was no significant graded correlation of Age with urine albumin excretion in inter-group and intra–group studies.

4. There was no significant difference in Blood Pressure in Microalbuminurics and Normalbuminurics.

5. There was no significant correlation of Blood Pressure with Urine Albumin Excretion in acute ischemic stroke.

6. Those with Electrocardiogram evidence of Left Ventricular Hypertrophy had significantly higher rate of urine albumin excretion.

SUMMARY

Microalbuminuria was long known to be a marker of early nephropathy. Its importance in other disease processes revealed itself in further studies. Its association with cerebrovascular diseases has been in focus in the last decade or so. This study may still be relevant since studies have been far and few between regarding this aspect in this part of the country.

The aim of the study was to assess the prevalence of microalbuminuria in acute ischemic stroke and to evaluate its prognostic significance. This study found a 47% prevalence of microalbuminuria in acute ischemic stroke after other factors which may confound it were excluded as far as possible. There was a significant association and correlation of microalbuminuria with the severity of the neurologic deficit so that it may be useful as a prognostic marker. Microalbuminurics were significantly older than normalbuminurics but the strongest correlation was with the severity of neurologic deficit.

Further studies are needed regarding this and other aspects of microalbuminuria with its emerging role as predictor of vascular incidents of heart, brain, kidney as well as in any disease process where blood vessels have a significant role.

BIBLIOGRAPHY

1) Yudkin JS, Forest RD, Jackson CA – Microalbuminuria as a predictor of vascular disease in non-diabetic subjects. Islington diabetics survey, Lancet, 1988; 2; 530-533.

2) Gould MM, Mohamed Ali V, Goubet SA, Yudkin JS, Haines AP – Microalbuminuria; association with height and sex in non-diabetic subjects: BMJ; 1993; 306; 240-243.

3) Guest GS, Ratnaike S, Larkins RG; Albuminuria in Aborigines and Euripides of Southeastern Australia: Med J Aust, 1993; 159' 335-338.

4) Schultz CJ, Konopelska-Bahu I, Dalton RN, Carroll TA, Stratton I, Gale EA, Neil A, Dunger DB: Diabetes Care; Volume 22, Issue 3; 495-502.

5) Hertzel C. Gerstein; Johannes FE Mann, Janice Pogua, Scan F Dinneen, Jean-Pierre Halle, Byren Hoogwerf; Garol Joyee, Andrew Rashkov, Janies Young; Bernard Zinman; Salim Yousuf; Diabetes Care: Volume 23 Supplement 2.

6) Gupta DK, Verma LK, Prevalence of Microalbuminuria in Indian Diabetics: Indian J Nephro 1991: 51-61.

7) Mykkanen L, Saccaro DJ, O'Leary DH, Howard G, Robbins DC, Haffner SM: Microalbuminuria and Carotid artery intima-media thickness in non diabetic and NIDDM subjects: The IRAS stroke, 1997; 28; 1710-1716.

8) Jalal S, Sofi FA, Alai MS, Siddiqqi MA, Bhat MA, Khan KA, Jan VM, Lone NA, Rather AA: Prevalence of Microalbuminuria in Essential Hypertension: Indian J Nephrology:2001;11:6-11.

9) Barmer NB, Coull BM, Clark WM, Wyan M: Microalbuminuria in Ischemic stroke: Arch Neurol, 1999;56;699-702.

10) Turaj W, Slowik A, Wyrwicz-Petkow U, Pankiewicz J, Iskra T, Rudzinska M, Szczudlik A; Prognostic significance of Microalbumunuria in non-diabetic stroke:Med Sci Monit, 2001;7(5); 989-994.

11) Jensen JS, Broch-Jonhnson K, Jensen G, Feldt-Rasmussen B; Atherosclerotic risk factors in health subjects with microalbuminuria;Atherosclerosis; 1995; 112:245-252.

12) Metcalf P, Baker j, Seragg RK, Dryson E, Seott A, Wild C: Albuminuria in Middleaged work force; clin chemic; 1993:39; 1793-1797.

13) Haffner SM, Stern MP, Gruber KK, Hazuda HP, Mitchell BD; Patterson JK: Microalbuminuria – Potential marker for increased cardiovascular risk factor in nondiabetic subjects: Arteriosclerosis; 1990; 10: 721-931.

14) Jensen JS, Feldt –Rasmussen B, Borch-Johnsen K, Clausen P, Appleyard M, Jensen G: Microalbumuniria and it relation to cardiovascular disease; J Hum Hypertention 1997; 11; 727-732.

15) Paul E.de Jong, Gary.C. Earbas: Screening, monitoring and

treatment of microalbuminuria; J Ame Soc Nephrol: 2006:17; 2120-2126.

16) M. Luiza Caramori, Young Ki Kim, Huang C, Fish AJ, Rich SS, Miller ME, Russel G, Masser M: Cellular Basis of Diabetic Nephropathy: Diabetes:2002:51:506-513.

17) Deckert T, Kofoed-Envoldson A, Norgaard K, Bosch-Johnsen K, Feldt-Rasmussen B, Jemen T: Microalbuminuria -Implication for Micro and Macrovascular disease:Diabetic Care 1992 ; Sep:15(9;1181-91)

18) Zenere BM, Arcario G, Saggiane F, Rossi L, Muggeo M, Lechi A: Noninvasive detection of functional alteration of the arterial wall in IDDM patients with and without microalbumunuria: Diabetic care: 1995:Vol.18, Issue 7; 975-982.

19) Dziedzic T, Slowik A, Szczudihk A: Urine Albumin Excretion in Acute Ischemic stroke; Clin Chem Lab Med 2004 Feb;42(2):182-5.

20) Turaj W, Slowik A, Szczudlhk A: Mechanism determining the occurence of Microalbumunuria in patients with acute ischemic stroke: Przegl Lek, 2001; 58(10): 889-93.

21) Pedrinelli R, Giampietro O, Carmassi F etal: Microalbuminuria and Endothelial dysfunction in essential Hypertension; Lancet; 1994; 344; 14-18.

22) Mogensen CE, Viberti GC, Peheim E, Kutter D, Hasslacher

C , Hoffman W, Renner R, Bojertig M, Poulsen PL, Scott G, Thoma J, Kuefer J, Nilsson B, Gambke B, Mueller P, Steinbiss J, Williamowski KD: Multicenter evaluation of the MICRAL-TEST strip; Diabetes Care; Vol 20; Issue 2; 1642-1646

23) Incerti J, Zelmanovitz T, Camergo JL, Luiz GJ, Azevedo DE: Evaluation of tests for Microalbuminuria screening: Nephrology Dialysis Transplantation; 2005; 20(11); 2402-2407

24) Jafar TH, Stark PC, Schmid CH, Landa M, Mascho G, de jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD study group; Progession of CKD; Ann Inter Med 139; 244-252;2003.

25) de Zeeuw D, Remuzzi G, Parving H H, Keare W F, Zhang Z, Shahinfar S, Snapino S, Brenner B M: Albuminuria –Therapeutic target for cardiovascular protection; Circulation; 110; 921-927;2004.

26) Lee DH, Dong-Wha Kang, Jae Sung Ahn, Chong Gon Choi, Sang Joon Kim, Dae Chul Suh ;Imaging of the ischemic Penumbra in acute stroke : Korean J Radiol 2005: 2006: 64-67

27) Razumovsky AY; value of TCD: htpp: www.neuro.neva.ru/English/issues/Articles2000/Razumovsky. Htm.

28) Bouousslavsky J, Leelere JR: Platelet Gp2b/3a inhibitors for acute ischemic stroke; Neurology; 2001; 57; 553-557

29) Keen H, Chlouverakis C: Urine albumin excretion and diabetes; Lancet; 1964; 14; 1155-1157

30) Vertin GC,Hill RD, Jarret RJ, Argyropoulos A, Mahmud U, Keen H: Microalbuminuria as a predictor of clinical nephropathy; Lancet;1982;(8287)1430-32

31) Hillege HL, Wilbert MT, Janssen Annet A.A.Bak, Giller IH Dierek, Diedrick E Grobber, Harry JGM Crijns, Wick H van Gilst, Dick de Zeeuw, Paul E de jong: Microalbuminuria in non-diabetic non hypertensive population; J Intern Med;2001;249;519-526

32) Weir CJ, Bradford APJ, Lees R: Prognostic values of the components of GCS following acute stroke; Q J Med; 2003;vol.96; no.1; 67-74

33) McKinnon KL, Molnar Z, Lowe D, Watson ID, Shearer E: Use of microalbuminuria as a predictor of outcome in critically ill patients; British Journal of Anesthesia; 2000; 84(2); 239-241

34) Perry P Ng, Randall T Higashida, Sean P Cutter, Reza Malik, Christopher F Doud, Van V Halbachi: Intraarterial Thrombolysis in acute ischemic stroke; Journal of Vascular and Interventional Radiology;2004;15;577-585

35) Evans G, Greaves I: Microalbuminuria as a predictor of

Outcome; BMJ; 1999;Jan23; 318(7178); 207-208

36) Pallister I, Gosling PT, Alpar EK, Bradley S: Predictor of post traumatic ARDS;J Trauma;1997;42;1056-1061

37) Shearman CP, Gosling P, Walker KJ: Proteinuria in Pancreatitis; J Clin Path; 1989; 42; 1132-35

38) Smith FCT, Gosling P, Sanghera K, Green MA, Paterson IS, Shearman CP: Microproteinuria predicts the severity of systemic effects of reperfusion injury following aortic surgery; Ann Vasc Surgery;1994;81-85

39) Roine I: Microalbuminuria-an index of severity of childhood meningitis; Pediatric Infectious Diseases J; 1993; 12; 584-588

40) Harrison's Textbook of Internal Medicine; 16th edition; 2378- 2379

41) Metcalf P, Baker J, Scott A, Wild C, Snagg R, Dryson E: Albuminuria in people at least 40 yrs old-Effects of obesity, Hypertension, Dyslipidaemia; Clin Chem 1992; 37; 1802-08

PROFORMA

Name:

Age:

Gender:

Address:

IP No:

Presenting illness:

Past History:

General Examination:

Vitals:

System Examination:

CNS: GCS:

Higher mental functions:

Cranial nerves:

Motor system:

Sensory system:

Autonomic nervous system:

Meningeal signs:

Skull and Spine:

CVS:

RS:

Abdomen:

Investigations:

Hematocrit

TC, DC, ESR

Blood urea, sugar, serum creatinine, serum electrolytes, Lipid profile

ECG

Chest X-ray

CT Brain

24 HRS Urine Albumin Excretion